Researchers identify genes behind uterine leiomyosarcoma

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In a new study, Yale Cancer Center researchers have defined the genetic landscape of uterine leiomyosarcomas (uLMS). Furthermore, using fully sequenced patient-derived xenografts, the team has preclinically validated new treatment modalities, which may point to new treatments for uterine cancer. Study results were published online in an early edition of the Proceedings of the National Academy of Science (PNAS).

Uterine cancer is the most common gynecologic malignancy and uterine leiomyosarcomas (uLMS) are highly lethal sarcomas arising from the myometrium, the smooth muscle layer of the uterus. They represent the most common type of uterine sarcomas, which overall account for three to seven percent of all uterine cancers. uLMS have poor prognosis and are characterized by aggressive biological behavior leading to early local and distant metastatic spread.

A collaborative team—which included researchers with expertise in gynecological cancer, genomics, pathology, pharmacology, and computational biology from the United States of America, South Korea, Spain, and Italy—identified a number of genes that are frequently mutated in uLMS. Using an integrated and comprehensive genetic approach, scientists identified multiple genes with recurrent alterations in uLMS including the homologous-recombination DNA-repair deficiency (HRD), the alternative lengthening of telomere (ALT), C-MYC/BET, and PI3K-AKT-mTOR pathway as potential targets.

"Using two fully sequenced patient-derived-xenografts (PDXs) harboring deranged C-MYC/BET and PTEN/PIK3CA pathways and/or an HRD signature, we found olaparib (PARPi), GS-626510 (BETi), and copanlisib (PIK3CAi) monotherapy to significantly inhibit in vivo uterine leiomyosarcomas growth," said senior author of the study Alessandro Santin, MD, Professor of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine and Disease Aligned Research Team Leader for the Gynecological Cancers Program at Yale Cancer Center and Smilow Cancer Hospital. "Our integrated genetic analysis combined with in vivo preclinical validation experiments suggests that a large subset of uLMS may potentially benefit from existing PARPi/BETi/PIK3CAi targeted drugs."

The team reported results from 83 women diagnosed with uLMS from the U.S. and Italy to determine the molecular basis of the tumor's aggressive behavior. They sequenced the genes from the tumors and identified mutations that are crucial for these tumors to grow. The team also studied the copy number variations—genes that are not mutated but are amplified in the tumors to give them a growth advantage over normal tissues as well as tumor RNA expression levels and gene fusion products.

"The establishment of 2 PDXs with different mutation profiles provided the opportunity for in vivo assessment of whether a mutation profile is predictive of drug response," said corresponding author Joseph Schlessinger, Ph.D., William H. Prusoff Professor and Chairman of the Department...
of Pharmacology at Yale School of Medicine and Co-Director of the Yale Cancer Biology Institute. "These preclinical validation studies have suggested new opportunities for personalized therapy."


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